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## Typical variant of takotsubo cardiomyopathy in oncological patients. Two case reports and review of the literature

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**Abstract:** Takotsubo cardiomyopathy (TCM) represents an acute systolic left ventricular dysfunction typically triggered by severe psychological or physical stress. Oncological patients due to emotional distress of the diagnosis, proinflammatory and prothrombotic nature of cancer and also physical stress often following complex anticancer therapies are at high-risk of TCM. Moreover, there are also few reports of TCM associated with oncological treatment, mostly chemotherapy. Recent data from large registries indicate a surprisingly high incidence of malignancy in TCM, significant differences in clinical characteristics and unfavorable short- and long-term clinical outcomes in this specific group of patients.

Therefore, we present two case reports of TCM that occurred during active anticancer therapy. Both women were admitted with suspicion of acute coronary syndrome. The first patient underwent mastectomy two years before due to hormone receptor-positive breast cancer and on admission she was during adjuvant hormonotherapy with tamoxifen. The admission of the second patient was preceded by fifteen fractions of adjuvant external beam radiotherapy due to intermediate-risk endometrial cancer after radical hysterectomy. Based on coronary angiography type I of acute coronary syndrome was excluded. Both patients negated stressful situations in the period immediately before the symptoms onset. Within hospital course baseline apical ballooning observed in both cases fully recovered and enabled subsequent completion of oncological treatment in accordance with adopted treatment protocols without recurrence of TCM. To our knowledge, presented cases are the first reports showing direct relationship between TCM and adjuvant hormonotherapy with tamoxifen or pelvic radiotherapy.

**Keywords:** takotsubo cardiomyopathy, acute coronary syndrome, hormonotherapy, radiotherapy, cardio-oncology.

## Introduction

Contemporarily cardiovascular and neoplastic diseases constitute the leading causes of death all over the world. Cardiovascular complications are also an important problem in cancer patients. The malignancy process and anticancer treatment are dynamically explored in current medical research. However, together with numerous achievements in oncology field which lead to higher survival rates, the cardio-oncology interrelation seems to be crucial for further improvement of the effectiveness of anticancer treatment, prognosis and patients' quality of life [1, 2].

In recent years takotsubo cardiomyopathy (TCM) has been proposed as one of the potential cardiac complications in oncological patients. Although, Joy *et al.* found that only 1.13% of 122 855 TCM patients had cancer [3], in other studies the prevalence of such coexistence was much higher (6.7–14.4%) [4, 5]. In a very recent International Takotsubo Registry (InterTAK) [6] malignancy was found in 16.6% of 1604 TCM patients. The most frequent type of malignancy was breast cancer, followed by tumors of gastrointestinal system, respiratory tract and internal sex organs. Long-term mortality was higher in TCM patients with malignancy without impact on short-term outcomes. In the subanalysis limited to oncological patients, long-term mortality was comparable between patients with TCM and acute coronary syndrome (ACS) [6].

Traditionally, the etiology of TCM is associated with severe psychological or physical stress [7]. Due to this fact it is named also as 'stress cardiomyopathy' or 'broken heart syndrome' with proven increased sympathetic stimulation and high catecholamines concentration. Also different mechanisms involved in TCM were proposed including endothelial dysfunction, severe vasospasm, estrogens deprivation or inflammatory activation [8]. However, the cause-effect relationships between TCM and malignancy remain unclear. In oncological patients, the TCM development might be the result of prolonged stressful situations, mostly associated with diagnosis of malignancy and inflammatory system activation as a result of tumor development or use of anticancer treatment. A review of the literature by Coen *et al.* indicates 5-fluorouracil as the most common molecule associated with TCM [9].

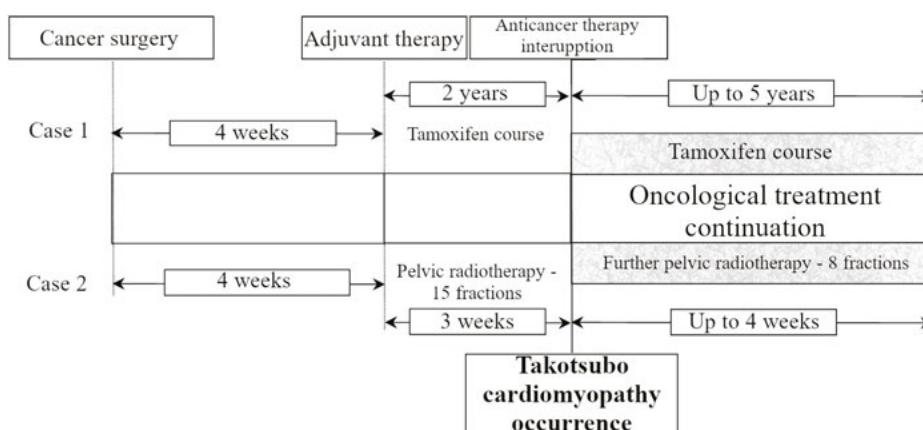
Despite the high proportion of post-menopausal women within TCM patients, none of the existing reports pointed sexual hormone deprivation during antiestrogen therapy with tamoxifen — standard treatment in hormone receptor-positive breast cancer — as a TCM cause. Surprisingly, although the radiotherapy is well-documented cardiovascular risk factor [1], we found in literature only one case report of thoracic region radiotherapy that induced TCM [10]. Therefore we sought to present two cases of co-occurrence of TCM and cancer in women, first during antiestrogen course with tamoxifen and second during pelvic radiotherapy. The report was prepared as the part of a project that was complied with the Declaration of Helsinki and was approved by the local Ethics Committee (Consent No. 1072.6120.59.2018). Written informed con-

sent was obtained from patients for the publication of the case reports and potentially-identifying information and images.

## Case reports

### Case 1

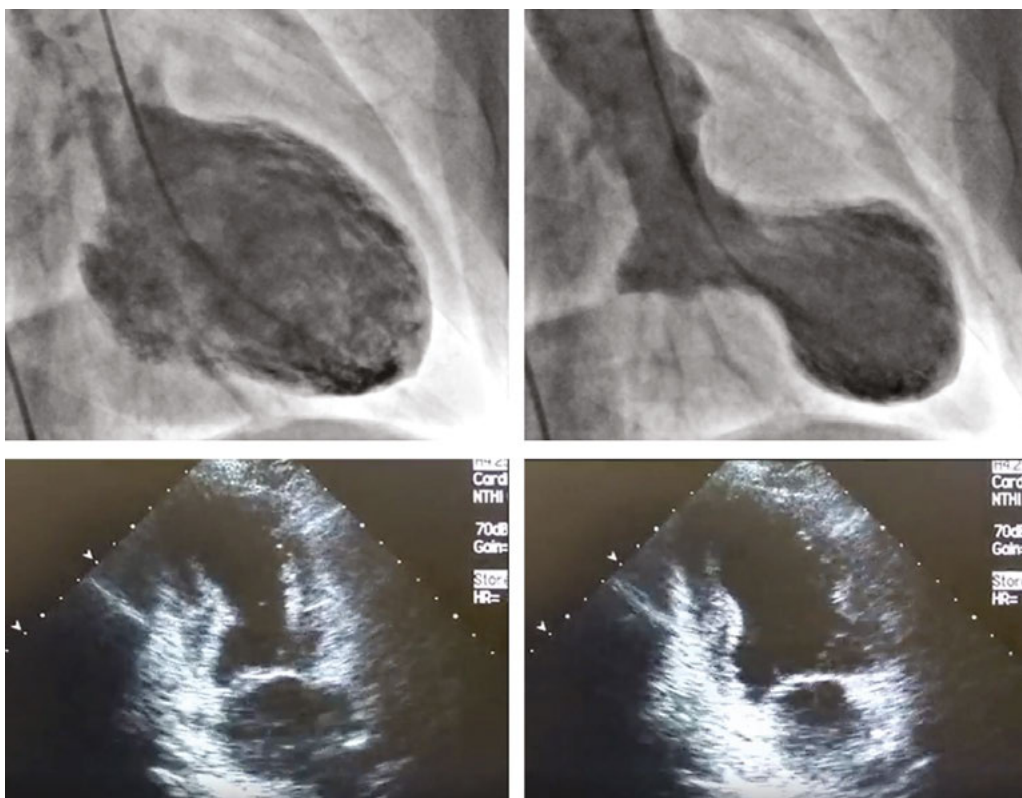
A 76-year-old woman with arterial hypertension and hypercholesterolemia was admitted with suspicion of ACS. Two years before she underwent resection of hormone receptor-positive left breast cancer followed by the adjuvant hormonotherapy with tamoxifen according to the current guidelines [11] (Fig. 1). ECG on admission revealed left axis deviation, the prolonged QT interval of 0.48 s, ST-segment elevation in III, aVF, V4-6 leads and flattened T wave in aVL and V1-2. All cardiac necrosis markers were elevated at baseline including isoenzyme MB of creatine kinase of 75 IU/L (upper limit of normal (ULN) <24 IU/L) and troponin I of 9.85 ng/mL (ULN <0.1 ng/mL). Immediately performed coronary angiography showed normal epicardial segments, with narrow distal part of left anterior descending artery [12, 13] (Fig. 2), while left ventricular (LV) angiography and transthoracic echocardiography (TTE) showed abnormal ballooning of apical segments with decreased ejection fraction up to 40% and hypertrophic intraventricular septum with obstruction of left ventricular outflow tract [14] (Fig. 3). Myocardial perfusion scintigraphy showed irreversible defect of technetium-99m uptake in apex and small reversible defect in periapical segments. The laboratory tests for pheochromocytoma including vanillylmandelic acid, metanephrine, normetanephrine and 3-methoxytyramine were unremarkable.



**Fig. 1.** Time course of oncological treatment and the occurrence of takotsubo cardiomyopathy in both patients.



**Fig. 2.** Normal epicardial coronary arteries with narrow distal part of left anterior descending artery. First case.

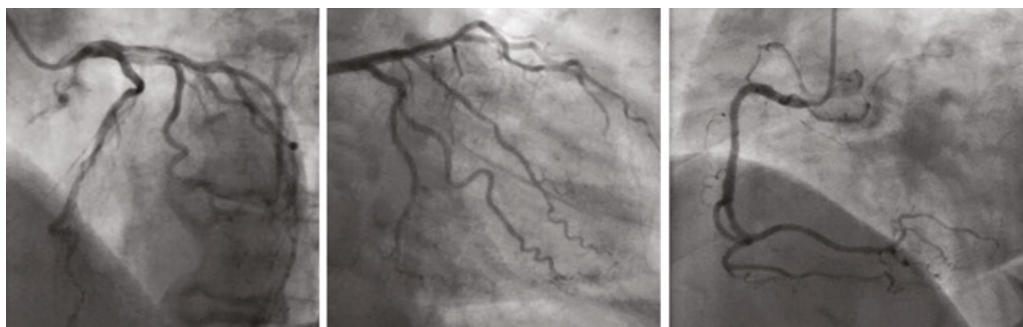


**Fig. 3.** Ventriculography and transthoracic echocardiography showing a typical ballooning of apex and peripical segments of left ventricle. First case.

Typical variant of TCM has been diagnosed according to the current criteria [8]. Apart from oncological treatment, our patient did not report any factors that could trigger TCM, therefore decision about the temporary withhold of oncological treatment was made (Fig. 1) with excellent effect and complete LV recovery in TTE. After 10 days from the onset of symptoms, tamoxifen therapy was resumed. The patient without any symptoms was discharged with detailed further follow-up plan [15]. After discharge, the patient has continued adjuvant hormonotherapy with tamoxifen up to 5 years without recurrence of TCM (Fig. 1).

## Case 2

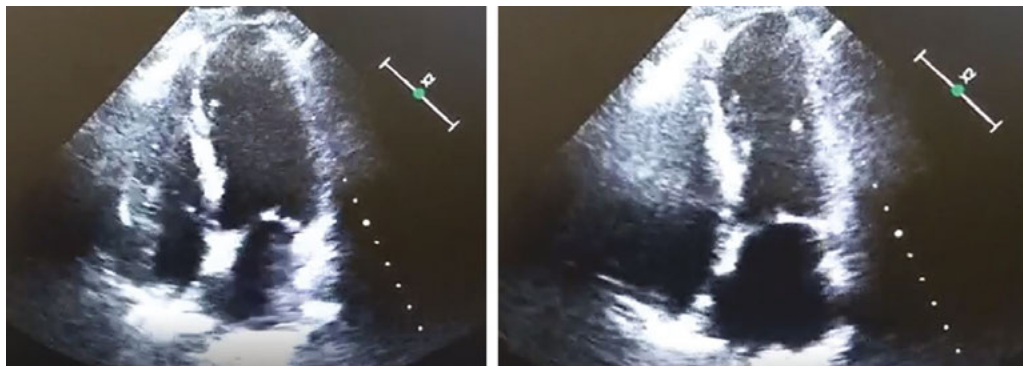
A 75-year old woman with arterial hypertension, hypercholesterolemia, impaired fasting glucose and obesity (body mass index of  $31.6 \text{ kg/m}^2$ ) was also admitted with suspicion of ACS. She had a history of radical hysterectomy with appendages due to intermediate-risk endometrial cancer followed by adjuvant radiotherapy 5 days a week for three weeks (30.0 Gy in 15 fractions) [16] (Fig. 1). In ECG on admission we found left axis deviation, PQ interval lasted 0.2 s and inversed T wave in V2-6 leads. The laboratory tests revealed normal level of isoenzyme MB of creatine kinase (19 U/l) but elevated troponin T concentration of 0.178 ng/mL (ULN <0.014 ng/mL). The coronary angiography showed normal, slightly tortuous epicardial arteries [12, 13] (Fig. 4),



**Fig. 4.** Normal, tortuous epicardial coronary arteries. Second case.

while TTE showed dyskinetic periapical ballooning of left ventricle (Fig. 5) with preserved global ejection fraction of about 50% [14]. The laboratory tests for pheochromocytoma were insignificant. Also in this case, the diagnosis of typical variant of TCM was diagnosed. The patient denied any stressful factor other than oncological treatment in the period preceding symptoms onset. During the hospital course complete recovery of left ventricular function was observed. After discharge, the patient

completed adjuvant radiotherapy in accordance with adopted treatment protocol (additional 8 fractions) without recurrence of TCM (Fig. 1).



**Fig. 5.** Left ventricular contractility with slightly dyskinetic apical segments visualized with transthoracic echocardiography. Second case.

## Discussion

The cases documented in this report exemplify the occurrence of typical variant of TCM in patients with neoplastic diseases. Moreover, they reflect the first well-documented cases of co-occurrence of TCM with tamoxifen hormone therapy or pelvic radiotherapy. In recent years, the direct association between malignancy and non-oncological comorbidities and their impact on outcomes have met with significant interest, especially among cardiovascular diseases [1, 17–19]. Also, studies on the relationship between TCM and neoplastic diseases have recently gathered the novel findings [3–7]. However, neither tamoxifen nor pelvic radiotherapy were pointed in current literature as TCM trigger. Importantly, in both presented patients the oncological therapy was resumed with satisfying outcomes despite the fact that the safety of anticancer therapy continuation in TCM survivors is still uncertain.

According to the recent data, the prevalence of cancer has been estimated between 1.1–16.6% of TCM patients [3–6]. The conclusions from the available studies lead to the recognition of these patients as a high-risk group with undoubtedly unfavorable prognosis. The InterTAK Registry indicates that TCM patients with malignancy required more frequently acute cardiac care ( $P = 0.007$ ), more often invasive respiratory support ( $P = 0.002$ ) and had higher long-term mortality ( $P < 0.001$ ) than others [6]. In turn, Joy *et al.* [3] showed higher incidence of in-hospital complications like tracheostomy or mechanical ventilation, higher in-hospital mortality (13.8 vs 2.9%,  $P < 0.0001$ ),



longer in-hospital stay (7 vs 4 days,  $P < 0.0001$ ) and higher total charges of hospitalization ( $P < 0.0001$ ) associated with TCM cancer patients. A recent meta-analysis by Brunetti *et al.* [4] confirmed previous findings of worse prognosis of malignancy-related TCM survivors expressed as increased risk of in-hospital events (RR 2.08, 95% CI 1.50–2.87,  $P < 0.01$ ) and follow-up adverse events (RR 3.30, 95% CI 3.09–3.51,  $P < 0.01$ ) as compared to TCM patients without cancer.

The unfavorable in-hospital and long-term outcomes in TCM patients with cancer make that discussion about this coincidence mechanism and subsequent prevention seems of vital importance. As mentioned above, the significance of stress in TCM development is well-documented [7, 8]. Cancer is a known trigger for strong emotional impulses, such as stress, fear or anxiety associated with diagnosis and treatment [20]. The excessive release of catecholamine as a result of high sympathetic stimulation is thought to cause microvascular dysfunction as well as occasional epicardial vasospasm [8]. The hypothesis of transient coronary artery blood flow impairment also in our breast cancer patient is supported by the result of scintigraphy. The vast majority of TCM survivors are post-menopausal women [7]. In this specific population significant decrease of estrogen level might be a potential explanation of catecholamine-mediated vasoconstriction [21]. The suggested mechanisms of cardiotoxic effects of estrogen deprivation are associated with reduction of endothelial nitric oxide synthase activity and promotion of endothelial apoptosis in response to vascular injuries [22]. As it has been emphasized in our report, the first presented patient was not only post-menopausal women but she additionally was treated with antiestrogen agent tamoxifen. The concentrations of sexual hormones could be extremely low in such patients and their deficiency might promote the development of TCM. On the other hand, there is evidence that tamoxifen improves endothelial function [23] and decreases the risk of myocardial infarction (RR 0.62; 95% CI, 0.41–0.93) [24] in contrast to anticancer agents with previously demonstrated relationship with TCM [9]. It is possible that these opposing properties of tamoxifen led to the lack of a similar clinical case presentation in the literature so far.

The association of radiotherapy and TCM occurrence was previously reported once in patient with breast cancer [10]. In the current report the second patient underwent pelvic radiotherapy. However, due to the difference of irradiated region, the another mechanisms probably led to TCM occurrence in both cases. An irradiation of a supradiaphragm region has been suggested as cardiovascular risk factor in numerous studies and pointed in last cardio-oncological guidelines of the European Society of Cardiology [1]. Recent studies provide arguments that endometrial cancer radiotherapy also increases the cardiovascular risk of thromboembolism (HR 2.07, 99% CI 1.57–2.72), pulmonary heart diseases (HR 1.74, 99% CI 1.26–2.40) or atrial fibrillation (HR 1.50, 99% CI 1.07–2.11) [25]. This increased thromboembolic risk in TCM patients may be associated with impaired perfusion of coronary microcircula-

tion [26–28]. Also our patient had slow epicardial flow and reduced myocardial perfusion [29, 30].

In case of patients with malignancy complicated by TCM, the issue of anticancer therapy continuation remains a clinical challenge. Coen's *et al.* [9] indicated that in majority of patients anticancer treatment was changed and only one third of patients who resumed the prior treatment safely completed therapeutic protocol. In our cases the initial anticancer therapy was successfully completed. However, the decision of protocol completion after TCM occurrence remains questionable. In case of our first patient, the tamoxifen protocol continuation up to five years is clearly recommended in current guidelines due to the better prognosis documented by Early Breast Cancer Trialists' Collaborative Group. The significant reduction of 15-years breast cancer recurrence ( $P < 0.001$ ) and mortality ( $P = 0.01$ ) in 5-years tamoxifen group as compared with 1–2-years tamoxifen protocols have been noticed [31]. Discontinuation of treatment at the time of TCM occurrence in our patient would worsen her long-term prognosis. Similarly, the completed adjuvant radiotherapy protocol significantly increased overall survival of patients with stage IC/grade 1 ( $P < 0.001$ ) and stage IC/grades 3 and 4 ( $P < 0.001$ ) of endometrial carcinoma [32]. Further prospective studies are required to provide reliable consensus of anticancer regimen resumption in TCM survivors.

## Conclusions

TCM is a possible cardiovascular complication of oncological treatment with evidenced serious prognosis. Despite the high prevalence of malignancy in TCM individuals, the pathogenesis of TCM and its relationship with cancer and anticancer treatment is still not fully elucidated. As shown above, tamoxifen as well as pelvic radiotherapy are a possible novel triggers of TCM that was fully reversible and was not a contraindication for further completion of anticancer treatment protocols.

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## Conflict of interest

None declared.



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